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10/526,697

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EXAMINER

BELYAVSKYI, MICHAEL A

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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES

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*Ex parte* MARK E. DUDLEY, STEVEN A. ROSENBERG,  
and JOHN R. WUNDERLICH

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Appeal 2010-010858  
Application 10/526,697  
Technology Center 1600

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Before ERIC GRIMES, MELANIE L. McCOLLUM, and  
STEPHEN WALSH, *Administrative Patent Judges*.

WALSH, *Administrative Patent Judge*.

DECISION ON APPEAL<sup>1</sup>

This is an appeal under 35 U.S.C. § 134(a) involving claims to a  
method of promoting cancer regression in a mammal by combining

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<sup>1</sup> The two-month time period for filing an appeal or commencing a civil  
action, as recited in 37 C.F.R. § 1.304, or for filing a request for rehearing,  
as recited in 37 C.F.R. § 41.52, begins to run from the “MAIL DATE”  
(paper delivery mode) or the “NOTIFICATION DATE” (electronic delivery  
mode) shown on the PTOL-90A cover letter attached to this decision.

chemotherapy and immunotherapy. The Patent Examiner rejected the claims as obvious. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

### STATEMENT OF THE CASE

The invention concerns “the combined use of immunotherapy and chemotherapy to promote the regression of a cancer in a mammal.” (Spec. [0001].)

Claims 23-40 are on appeal. Claim 23 is representative and reads as follows:

23. A method of promoting the regression of a cancer in a mammal, which method comprises:
- (i) administering to the mammal nonmyeloablative lymphodepleting chemotherapy, and
  - (ii) subsequently administering:
    - (a) autologous T-cells, which have been previously isolated and selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, and, either concomitantly with the autologous T-cells or subsequently to the autologous T-cells, by the same route or a different route, a T-cell growth factor that promotes the growth and activation of the autologous T-cells, or
    - (b) autologous T-cells, which have been previously isolated, selected for highly avid recognition of an antigen of the cancer, the regression of which is to be promoted, by stimulation of the T-cells *in vitro* with the antigen of the cancer, and modified to express a T-cell growth factor that promotes the growth and activation of the autologous T-cells, followed by one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody, and IL-2, whereupon the regression of the cancer in the mammal is promoted.

The Examiner rejected the claims as follows:

- claims 23-35, 37, and 38 under 35 U.S.C. § 103(a) as unpatentable over Dudley<sup>2</sup> or Gruenberg<sup>3</sup> (WO 97/05239), each in view of Slavin,<sup>4</sup> Riddell,<sup>5</sup> and Rosenberg;<sup>6</sup> and
- claims 36, 39, and 40 under 35 U.S.C. § 103(a) as unpatentable over Dudley or Gruenberg (WO 97/05239), in view of Slavin, Riddell, and Rosenberg, and further in view of Kawakami<sup>7</sup> and Stevens.<sup>8</sup>

## OBVIOUSNESS

### *The Issues*

For both grounds of rejection, the Examiner relied upon a combination of Dudley or Gruenberg, with Slavin, Riddell, and Rosenberg. The Examiner's position is that Dudley taught a method of promoting the regression of melanoma which comprised administering an autologous T cell

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<sup>2</sup> Mark E. Dudley et al., *Adoptive Transfer of Cloned Melanoma-Reactive T Lymphocytes for the Treatment of Patients with Metastatic Melanoma*, 24 J. IMMUNOTHERAPY, no. 4, 363-373 (2001).

<sup>3</sup> Int'l Publication No. WO 97/05239 by Micheal L. Gruenberg, published Feb. 13, 1997.

<sup>4</sup> US Patent No. 6,447,767 B1 issued to Shimon Slavin et al., Sep. 10, 2002.

<sup>5</sup> Stanley R. Riddell et al., *The use of anti-CD3 and anti-CD28 monoclonal antibodies to clone and expand human antigen-specific T cells*, 128 J. IMMUNOLOGICAL METHODS, 189-201 (1990).

<sup>6</sup> US Patent No. 5,126,132 issued to Steven A. Rosenberg, Jun. 30, 1992.

<sup>7</sup> Kawakami et al., *Identification of a human melanoma antigen recognized by tumor-infiltrating lymphocytes associated with in vivo tumor rejection*, 91 PROC. NATL. ACAD. SCI., 6458-6462 (1994).

<sup>8</sup> Emily J. Stevens et al., *Generation of Tumor-Specific CTLs from Melanoma Patients by Using Peripheral Blood Stimulated with Allogeneic Melanoma Tumor Cell Lines*, 154 J. IMMUNOLOGY, 762-771 (1995).

previously isolated, selected for highly avid recognition of melanoma antigen, and expanded in vitro. (Ans. 3.) The Examiner found that Dudley also disclosed subsequently administering IL-2 at various dosages (125,000 IU/kg and 720,000 IU/kg) to the same patient. (*Id.*) The Examiner found that Dudley also disclosed that some patients additionally received the MART-1 peptide. (*Id.*) According to the Examiner, Dudley taught that the poor persistence of adoptive transfer of T cells could be overcome by considering variations on the patient treatment protocol, including lymphodepleting chemotherapy. (*Id.* at 3-4.) The Examiner found that Dudley taught that such chemotherapy might improve lymphocyte survival and treatment efficacy. (*Id.* at 4.)

The Examiner found that Gruenberg taught a method of promoting the regression of cancer in a mammal comprising administering to a mammal autologous T-cells which have been stimulated in vitro with antigen of the cancer being treated, and administering IL-2 to the same patients at various concentrations. (*Id.*)

According to the Examiner, the instantly claimed invention differs from Dudley or Gruenberg in that these references did not explicitly teach administering non-myeloablative lymphodepleting chemotherapy prior to administering autologous T-cells which had been selected for highly avid recognition of melanoma antigen, stimulated in vitro with the antigen of the cancer, and subjected to one cycle of rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2. (*Id.*)

The Examiner's position is that Slavin taught a method of treating melanoma patients, comprising administering to the patient non-myeloablative treatment, including administering cyclophosphamide and

fludarabine prior to administering hematopoietic cells. (*Id.*) The Examiner found that Slavin disclosed using the non-myeloablative treatment to overcome the poor persistence of adoptive transfer of T-cells. (*Id.*) Additionally, the Examiner found that Slavin taught that the hematopoietic cells administered may contain T-cells and that T-cell depletion of donor stem cell preparations has been known to increase the risk of graft rejection. (*Id.*) Thus, according to the Examiner, Slavin established that at the time of the invention one of ordinary skill in the art would have known that administering nonmyeloablative lymphodepleting chemotherapy to a mammal was a routinely used method of inducing donor specific tolerance in a method of treating cancer, including melanoma. (*Id.* at 5.)

The Examiner found that Rosenberg taught a method of treating cancer, including melanoma, comprising administering to a patient an effective amount of autologous tumor infiltrating lymphocytes. (*Id.*) According to the Examiner Riddell taught a general methodology for determining an effective amount of said cells and also taught that the preferred amount is from about  $5 \times 10^9$  to  $5 \times 10^{11}$  cells. (*Id.*)

The Examiner found that Riddell taught an in vitro method of growing and expanding a large number of antigen specific T cells comprising rapid expansion using irradiated allogeneic feeder cells, OKT3 antibody and IL-2. (*Id.*) The Examiner found that Riddell disclosed an alternative culture method to clone and propagate human T cells that permitted retention of antigen specificity but did not require restimulation with antigen. (*Id.*) The Examiner found that Riddell disclosed that the expanded antigen-specific T-cells would be useful for adoptive immunotherapy. (*Id.*) According to the Examiner, Riddell shows that at the time of the invention a skilled artisan

would have known how to expand antigen specific T-cells using irradiated allogeneic feeder cells, OKT3 antibody and IL-2. (*Id.*)

The Examiner found that all the claimed elements were disclosed in the prior art and that a skilled artisan at the time of the invention would have found it obvious to combine these known elements for their known functions to yield predictable results. (*Id.*) Specifically, the Examiner found that a skilled artisan at the time of the invention would have found it obvious to combine the prior art teachings to obtain a method of promoting the regression of cancer in a mammal comprising administering non-myeloablative lymphodepleting chemotherapy comprising administration of cyclophosphamide and fludarabine prior to administering autologous T-cells which had been previously isolated, selected for highly avid recognition of melanoma antigen and expanded in vitro. (*Id.* at 6.) The Examiner reasoned that the artisan would have been motivated to do so to overcome the poor persistence of adoptive transfer of T-cells. (*Id.*)

Appellants contend that “[t]he combination of cited references ... fails to teach or suggest a method of promoting the regression of a cancer in a mammal comprising administering T cells which have undergone *one* cycle of rapid expansion, as claimed in claim 23.” (App. Br. 4; Reply Br. 2.)

In particular, Appellants assert that “Riddell teaches away from using one cycle of rapid expansion” by teaching that successful adoptive immunotherapy requires large numbers of T-cells obtained through the use of repetitive stimulation with anti-CD3. (App. Br. 4; Reply Br. 3.) According to Appellants, Riddell’s teachings suggested that “a single rapid expansion would not be expected to generate large enough numbers of T cells for successful adoptive immunotherapy.” (App. Br. 5.)

Appellants also assert that secondary considerations rebut any alleged prima facie case of obviousness. (*Id.*) In particular, Appellants assert that the Declaration of Dr. Mark E. Dudley, along with Example 1 in the instant application, and studies published in peer-reviewed journals establish that the presently claimed method provides unexpectedly superior clinical results over prior art methods. (*Id.* at 5-6.) Appellants assert that these materials disclosed that methods using multiple rounds of rapid expansion failed to provide T-cells that persisted in the bloodstream of patients and provided poor objective clinical results. (*Id.* at 6.) According to Appellants, in view of these results, “one of ordinary skill in the art would logically attempt to improve the persistence and effectiveness of the T-cells by *increasing* the number of cycles of rapid expansion, not [by] *decreasing* the number of cycles to one, as claimed.” (*Id.*) Additionally, Appellants assert that the Dudley Declaration explains that the claimed method answered a long-felt need in the art to treat patients by successfully producing positive objective clinical results in patients using a treatment method wherein the T-cells undergo one cycle of rapid expansion. (*Id.* at 7.) Based upon this same evidence, Appellants assert that the Declaration established that the claimed method succeeds where other methods have repeatedly failed. (*Id.* at 8.)

The issues with respect to these rejections are:

(a) whether the Examiner established that a skilled artisan at the time of the invention would have found it obvious over the combined prior art to administer autologous T-cells following one cycle of rapid expansion, as recited in the claimed method, and if so,

(b) whether Appellants provided evidence of secondary considerations such that the totality of evidence weighs in favor of nonobviousness.



*Finding of Fact*

We agree with the Examiner's explicit findings regarding the scope and content of the prior art references (Ans. 3-7), with one exception that we discuss in the Analysis below.

*Principles of Law*

In rejecting claims under 35 U.S.C. § 103, the Examiner bears the initial burden of presenting a prima facie case of obviousness. *See In re Rijckaert*, 9 F.3d 1531, 1532 (Fed. Cir. 1993).

It is well-established that a conclusion that the claimed subject matter is prima facie obvious must be supported by evidence, as shown by some objective teaching in the prior art or by knowledge generally available to one of ordinary skill in the art that would have led that individual to combine the relevant teachings of the references to arrive at the claimed invention. *See In re Fine*, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

*Analysis*

While we agree with the Examiner's explicit findings of fact regarding the disclosures of the prior art, we do not agree that "[a]ll the claimed elements were known in the prior art...." (*See* Ans. 5.) As Appellants have correctly asserted, the Examiner has not established, or even alleged, that the prior art taught administering T cells which have been subjected to *one* cycle of rapid expansion, as claimed. (*See* Reply Br. 2.) The Examiner addresses this claim limitation in the Response by stating that "one skilled in the art would expect that T cells that were subject to only one cycle of rapid expansion of T cell would produce[] clinical response in

patients” because the prior art taught that non-myeloablative treatment may be used to overcome the poor persistence of adoptive transferred T cells. (Ans. 11.) However, this reasoning was not provided as a basis for the rejection, and does not appear to have an evidentiary foundation. The cited prior art provided a suggestion to combine non-myeloablative chemotherapy with adoptive immunotherapy in a method of promoting cancer regression. What is missing is how these teachings, or the ordinary skill in the art, would have *additionally* suggested to the skilled artisan the further step of modifying the prior art methods by administering T-cells following only one cycle of rapid expansion. Without this evidence, the Examiner has not sufficiently supported a conclusion of prima facie obviousness. *See Rijckaert*, 9 F.3d at 1532; *Fine*, 837 F.2d at 1074.

Because the Examiner has not established prima facie obviousness, we do not need to discuss Appellants’ evidence of secondary considerations. (*See App. Br.* 5-10.)

### CONCLUSION OF LAW

The Examiner has not established that a skilled artisan at the time of the invention would have found it obvious over the combined prior art to administer autologous T-cells following one cycle of rapid expansion, as recited in the claimed method.

### SUMMARY

We reverse the rejection of claims 23-35, 37, and 38 under 35 U.S.C. § 103(a) as unpatentable over Dudley or Gruenberg, each in view of Slavin, Riddell, and Rosenberg;

Appeal 2010-010858  
Application 10/526,697

we reverse the rejection of claims 36, 39, and 40 under 35 U.S.C.  
§ 103(a) as unpatentable over Dudley or Gruenberg, in view of Slavin,  
Riddell, and Rosenberg, and further in view of Kawakami and Stevens.

REVERSED

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